

Effectiveness of disease-specific cognitive-behavioural therapy on depression, anxiety, quality of life and the clinical course of disease in adolescents with inflammatory bowel disease: study protocol of a multicentre randomised controlled trial (HAPPY-IBD)

Gertrude van den Brink,¹ Luuk Stapersma,² Hanan El Marroun,² Jens Henrichs,³ Eva M Szigethy,⁴ Elisabeth MWJ Utens,² Johanna C Escher,¹

To cite: van den Brink G, Stapersma L, El Marroun H, *et al*. Effectiveness of disease-specific cognitive-behavioural therapy on depression, anxiety, quality of life and the clinical course of disease in adolescents with inflammatory bowel disease: study protocol of a multicentre randomised controlled trial (HAPPY-IBD). *BMJ Open Gastro* 2016;**3**: e000071. doi:10.1136/bmjgast-2015-000071

GvdB and LS contributed equally and share first authorship.

Received 4 November 2015
Revised 11 December 2015
Accepted 21 December 2015

For numbered affiliations see end of article.

Correspondence to Professor Johanna C Escher; j.escher@erasmusmc.nl

ABSTRACT

Introduction: Adolescents with inflammatory bowel disease (IBD) show a higher prevalence of depression and anxiety, compared to youth with other chronic diseases. The inflammation-depression hypothesis might explain this association, and implies that treating depression can decrease intestinal inflammation and improve disease course. The present multicentre randomised controlled trial aims to test the effectiveness of an IBD-specific cognitive-behavioural therapy (CBT) protocol in reducing symptoms of subclinical depression and anxiety, while improving quality of life and disease course in adolescents with IBD.

Methods and analysis: Adolescents with IBD (10–20 years) from 7 hospitals undergo screening (online questionnaires) for symptoms of depression and anxiety. Those with elevated scores of depression (Child Depression Inventory (CDI) ≥ 13 or Beck Depression Inventory (BDI) II ≥ 14) and/or anxiety (Screen for Child Anxiety Related Disorders: boys ≥ 26 , girls ≥ 30) receive a psychiatric interview. Patients meeting criteria for depressive/anxiety disorders are referred for psychotherapy outside the trial. Patients with elevated (subclinical) symptoms are randomly assigned to medical care-as-usual (CAU; n=50) or CAU plus IBD-specific CBT (n=50). Main outcomes: (1) reduction in depressive and/or anxiety symptoms after 3 months and (2) sustained remission for 12 months. Secondary outcomes: quality of life, psychosocial functioning, treatment adherence. In addition, we will assess inflammatory cytokines in peripheral blood mononuclear cells and whole blood RNA expression profiles. For analysis, multilevel linear models and generalised estimating equations will be used.

Ethics and dissemination: The Medical Ethics Committee of the Erasmus MC approved this study. If we prove that this CBT improves emotional well-being

as well as disease course, implementation is recommended.

Trial registration number: NCT02265588.

BACKGROUND

Inflammatory bowel disease (IBD; Crohn's disease (CD) and ulcerative colitis (UC)) is a chronic relapsing inflammatory disorder of the intestine, with increasing incidence and prevalence worldwide.¹ Patients have abdominal pain, bloody diarrhoea, often accompanied by systemic symptoms such as lack of appetite, weight loss and fatigue. IBD has a fluctuating course, with relapses (increased disease activity) and periods of clinical remission. In up to 25% of patients, IBD manifests during late childhood and adolescence.^{2–4} Adolescence is a challenging life phase, with significant psychological, physical and social changes. Having IBD during adolescence is a threat to healthy psychosocial development, making transition to adulthood more difficult.

Adolescent patients with IBD frequently experience psychological and social problems.⁵ They often have low self-esteem and report stress concerning their disease and future.⁶ In addition, their quality of life is reduced^{2 7 8} due to the unpredictable course of disease, embarrassing symptoms, frequent hospital visits or admissions and (side effects of) medical treatment. Furthermore, the possible extra intestinal manifestations (eg,



primary sclerosing cholangitis, arthritis), complications (eg, strictures) and surgical treatments (eg, resections) reduce quality of life significantly.^{2 8–12}

Depressive symptoms are common, and occur in 20–40% of adolescents with IBD.^{13–18} Anxiety, reported in 30–50% of adolescents with IBD, is even more common.^{7 19} In many young patients, symptoms of depression and anxiety occur together.^{20 21} Not surprisingly, early onset of mental health problems can predict poor long-term medical and psychological outcomes.^{22–24}

Taken together, it is clear that psychological problems are often found in young patients with IBD. The inflammation–depression hypothesis has been proposed to explain the association between psychological problems and IBD, and implies that treating emotional symptoms can decrease intestinal inflammation, and thus, improve disease course.²⁵ This hypothesis will be discussed in detail later in this paper.

Factors associated with depression and anxiety in IBD

Medical, psychological and family factors are associated with depression and anxiety in IBD and can influence the effectiveness of treatment of emotional problems in IBD. Known medical factors are: being recently diagnosed with IBD,²⁶ a diagnosis of CD (vs UC),²⁷ a history of surgery,^{27 28} active disease,^{26–32} non-adherence to therapy³¹ and IBS (like) symptoms.³³ Psychological factors are: high levels of perceived stress,²⁶ negative cognitive coping,¹⁵ low self-esteem^{8 34} and sleep disturbance.³² Family factors are: parental stress,^{35 36} low socioeconomic status,^{26 27 31} stressful life events³⁷ and unhealthy family functioning.^{10 34 37} In paediatric patients, active disease^{15 18 19 38 39} and low socioeconomic status¹⁵ are associated with depression and/or anxiety.

In the opposite direction, emotional problems have also been shown to influence disease activity. Psychological stress can trigger a relapse in IBD^{30 40–44} and lead to a more difficult-to-treat (refractory) disease.³⁰ Moreover, emotional problems decrease the ability to cope with physical symptoms, increase the sensitivity to abdominal pain,⁴⁵ increase medical service use and decrease therapy adherence.^{16 19 29 46 47}

Altogether, these findings emphasise the existence of a bidirectional relationship between emotional problems and disease activity in patients with IBD. We therefore expect that early recognition and treatment of emotional problems is necessary to improve both mental health and the clinical course of disease.

Inflammation–depression hypothesis

The ‘inflammation–depression hypothesis’ or ‘brain–gut hypothesis’ proposes that intestinal inflammation, by means of increased production of proinflammatory cytokines (eg, tumour necrosis factor α (TNF- α)), is known to directly and indirectly affect the brain and thereby increase symptoms of depression.⁴⁸ It is also suggested

that psychological stress can increase depressive symptoms by increasing inflammation.^{25 48 49}

Most evidence for this hypothesis comes from animal studies in which experimental (psychological) stress has shown to induce and reactivate inflammation in colitis models.⁴⁴ It is suggested that these stress-induced alterations in inflammation are mediated through changes in hypothalamic–pituitary–adrenal axis function, and alterations in bacterial mucosal interactions.^{25 44 50–52} Similarly, human studies also show the proinflammatory effect of experimental^{25 50} and (early) life stress,⁵² and show elevated levels of inflammatory markers in depressed patients.^{49 53–56}

There are few paediatric IBD studies examining the relationship between inflammation and depression.⁴⁸ Furthermore, the brain–gut hypothesis mainly focuses on depression, the relation between inflammation and anxiety has been studied less extensively.⁵⁷ Reviews by Hou and Baldwin⁵⁸ and Salim *et al*⁵⁹ show the existing evidence in animal models linking inflammation with anxiety. In humans, a chronic anxiety state has been shown to negatively affect immune function, and several studies report a positive correlation between anxiety and increased inflammatory markers.^{57–60} To the best of our knowledge, little is known about the association between anxiety and inflammation in IBD. The present study will contribute to more understanding of this association.^{19 31}

CBT for adolescents with IBD

From all different psychotherapies, cognitive–behavioural therapy (CBT) is the most evidence-based psychotherapy to reduce symptoms of anxiety and depression.^{12 61 62}

For adolescents with IBD, Szigethy *et al*⁶³ developed a disease-specific CBT programme called PASCET-PI (Primary and Secondary Control Enhancement Training—Physical Illness) (see Intervention section). They performed a randomised controlled trial (RCT) (2007) in adolescents with IBD and subclinical depression (total N=41). A 40% reduction in depressive severity in the PASCET-PI group was found compared to the control group, receiving care-as-usual (CAU).¹⁷ These positive effects were maintained 1 year after treatment.²³ However, anxiety was not addressed. Only a few paediatric studies have integrated the clinical course of disease or disease activity as an outcome parameter. Szigethy *et al*⁶⁴ compared the effect of two different psychotherapies in paediatric patients with IBD with (sub)clinical depression and found that both therapies had a significant impact in improving depression, while CBT was associated with a greater reduction in disease activity. Reigada *et al*⁶⁵ showed in a CBT-pilot with nine (paediatric) patients and only comorbid anxiety, that 90% no longer had an anxiety disorder and half the patients had a reduction in IBD severity.

Although the aforementioned studies showed promising results, larger scale randomised studies are necessary to evaluate the longitudinal effect of CBT in paediatric

IBD, and to identify potential moderators of CBT success. To the best of our knowledge, at present, there are no RCTs assessing simultaneously the effect of CBT on the two psychological outcomes (symptoms of depression or anxiety) and the clinical course of disease in adolescents with IBD.

Aim and hypothesis

The aim of the present study is to test the effectiveness of the disease-specific CBT programme (PASCET-PI) in reducing symptoms of depression *and* anxiety in adolescents with IBD in order to improve quality of life and to improve the clinical course of disease. We hypothesise that the PASCET-PI will reduce symptoms of both depression and anxiety, improve quality of life, reduce intestinal inflammation and will promote sustained clinical remission.

METHODS AND DESIGN

Study design

This study is a prospective, multicentre, RCT, with baseline screening (T0) and three follow-up assessments (T1–T3). At baseline, adolescents (aged 10–20 years) with IBD are screened for symptoms of depression and anxiety by means of an online questionnaire. Patients with elevated (subclinical) symptoms of depression and/or anxiety, but no clinical disorder, are randomised into two conditions. The control condition entails standard medical CAU; psychological care is not standard in the Dutch medical care system. Patients in the experimental condition receive standard medical care plus the disease-specific CBT (PASCET-PI). Patients are recruited from two academic hospitals and five community hospitals in the South-West region of the Netherlands¹. The design of this study is following the CONSORT guidelines for RCTs.

Inclusion and exclusion criteria

Inclusion criteria are: (1) patients between 10 and 20 years of age with diagnosed IBD and (2) informed consent provided by patients and (if applicable) parents.

Exclusion criteria are: (1) mental retardation (parent report); (2) current psychopharmacological treatment for depression or anxiety; (3) current psychological treatment; (4) having received manualised CBT in the past year (at least 8 sessions); (5) insufficient mastery of the Dutch language; (6) diagnosed bipolar disorder, schizophrenia/psychotic disorder, autism spectrum disorders, obsessive-compulsive disorder, post-traumatic, acute stress-disorder or substance use disorder; (7) selective mutism (physician reported) and (8) already participating in an intervention study.

Recruitment and procedure

See figure 1 for an overview of the procedure. The treating (paediatric) gastroenterologist, nurse practitioner or physician assistant informs eligible patients about this study and hands out the written patient information. Parents are asked for informed consent if patients are younger than 18 years; if patients aged 18 years or older still live in their parents' house, participation of parents is optional. After having given informed consent, patients (and parents) receive an e-mail with online questionnaires (table 1). If this screening shows self-reported subclinical symptoms of depression and/or anxiety, a patient is selected for further participation in the study. The Dutch versions of the Child Depression Inventory (CDI; ages 10–17 years),⁶⁶ Beck Depression Inventory (BDI-II; ages 18–20 years),⁶⁷ are used to assess

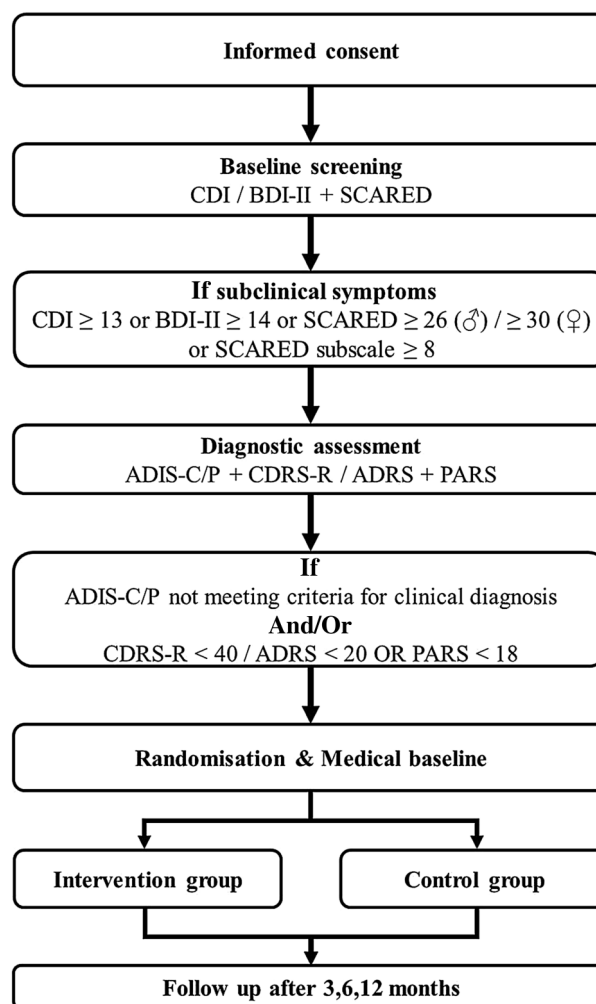


Figure 1 Flow chart study design (ADIS-C/P, Anxiety Disorders Interview Schedule—Child and Parent Version; ADRS, Adolescent Depression Rating Scale; BDI-II, Beck Depression Inventory—Second Edition; CDI, Child Depression Inventory; CDRS-R, Child Depression Rating Scale—Revised; PARS, Pediatric Anxiety Rating Scale; SCARED, Screen for Child Anxiety Related Emotional Disorders).

¹Erasmus MC(-Sophia), Leiden University Medical Centre (LUMC), Haga (Juliana Children's) Hospital, Reinier de Graaf Gasthuis, Maastad Hospital, Amphia Hospital, and Albert Schweitzer Hospital.

**Table 1** Outcomes, covariates, instruments and informants at each time point

Measurements	T0 baseline	T1 3 months	T2 6 months	T3 12 months
<i>Main psychological outcomes</i>				
Change in symptoms of depression				
CDI (10–17 year)	Pt	Pt	Pt	Pt
BDI-II (18–20 year)	Pt	Pt	Pt	Pt
ADIS-C/P	Pt, Pr	Pt, Pr	Pt, Pr	Pt, Pr
CDRS-R (10–12 year)	Ps	Ps	Ps	Ps
ADRS (13–20 year)	Ps	Ps	Ps	Ps
Change in symptoms of anxiety				
SCARED	Pt	Pt	Pt	Pt
ADIS-C/P	Pt, Pr	Pt, Pr	Pt, Pr	Pt, Pr
PARS	Ps	Ps	Ps	Ps
<i>Main medical outcome</i>				
Sustained remission				M
<i>Secondary psychological outcomes</i>				
(Change in) Quality of life				
TACQOL (10–15 year) ⁷⁶	Pt	Pt	Pt	Pt
TAAQOL (16–20 year) ⁷⁷	Pt	Pt	Pt	Pt
IMPACT-III ⁷⁸	Pt	Pt	Pt	Pt
(Change in) Psychosocial functioning				
SSRS ⁷⁹	Pt	Pt	Pt	Pt
YSR (10–17 year) ⁸⁰	Pt	Pt	Pt	Pt
ASR (18–20 year) ⁸¹	Pt	Pt	Pt	Pt
<i>Secondary medical outcomes</i>				
(Change in) Disease activity				
PUCAI (ulcerative colitis)	M	M	M	M
PCDAI (Crohn's disease)	M	M	M	M
Physician Global Assessment ⁴⁶	M	M	M	M
Inflammatory markers				
CRP	Pt	Pt	Pt	Pt
ESR	Pt	Pt	Pt	Pt
Faecal calprotectin	Pt	Pt	Pt	Pt
Use of IBD medication				
Steroids, anti-TNF blockers, immunomodulators	M	M	M	M
Necessity of surgical intervention	M	M	M	M
<i>Psychological covariates</i>				
Demographic factors				
Rotterdam's quality of life interview ⁸²	Pr			
Illness perception				
B-IPQ ⁸³	Pt	Pt	Pt	Pt
Cognitive coping styles				
CERQ ⁸⁴	Pt	Pt	Pt	Pt
Quality of sleep				
SSR ⁸⁵	Pt, Pr	Pt, Pr	Pt, Pr	Pt, Pr
Parental anxiety and depression				
DASS-21 ⁸⁶	Pr			
Life events				
Stress scale thermometer ⁸⁷	Pt, Pr	Pt, Pr	Pt, Pr	Pt, Pr
Life events questionnaire from CERQ	Pt			Pt
Family functioning				
FAD-GF ⁸⁸	Pr	Pr	Pr	Pr
<i>Medical covariates</i>				
Disease phenotypes				
Medical file analysis using Paris Classification	M			
Treatment strategy				
Report of treating physician/medical file analysis	M	M	M	M
IBS-like symptoms				
Questionnaire based on Rome III criteria IBS	M	M	M	M

Continued

Table 1 Continued

Measurements	T0 baseline	T1 3 months	T2 6 months	T3 12 months
RNA expression profiles				
Blood sample	M	M		
Cytokine levels in plasma and peripheral blood mononuclear cells (PMBCs)				
Blood sample	M	M		

M, medical file/(paediatric) gastroenterologist; Pr, parent report; Ps, psychologist; Pt, patient (self-report). ADIS-C/P, Anxiety Disorders Interview Schedule—Child and Parent Version; ADRS, Adolescent Depression Rating Scale; ASR, Adult Self-Report; BDI-II, Beck Depression Inventory—Second Edition; B-IPQ, Brief—Illness Perception Questionnaire; CDI, Child Depression Inventory; CDRS-R, Child Depression Rating Scale—Revised; CERQ, Cognitive Emotion Regulation Questionnaire; CRP, C reactive protein; DASS-21, Depression, Anxiety and Stress Scale—21-item version; ESR, erythrocyte sedimentation rate; FAD-GF, Family Assessment Device—General Functioning scale; IBD, inflammatory bowel disease; IBS, Irritable Bowel Syndrome; PARS, Pediatric Anxiety Rating Scale; PCDAI, Pediatric Crohn's Disease Activity Index; PMBC, peripheral blood mononuclear cells; PUCAI, Pediatric Ulcerative Colitis Activity Index; SCARED, Screen for Child Anxiety Related Emotional Disorders; SSR, Sleep Self-Report; SSRS, Social Skills Rating System; TAAQOL, TNO-AZL questionnaire for Adult health-related Quality Of Life; TACQOL, TNO-AZL questionnaire for Children's health-related Quality Of Life; TNF, tumour necrosis factor; YSR, Youth Self-Report.

depressive symptoms, whereas the Screen for Child Anxiety Related Disorders (SCARED; ages 10–20)⁶⁸ is used to assess anxiety symptoms. Subclinical depressive symptoms are defined as a score equal to or above the cut-off on the CDI (13)⁶⁶ or the BDI-II (14).⁶⁷ Subclinical anxiety symptoms are defined as: (1) a score equal to or above the cut-off on the total scale of the SCARED (26 for boys, 30 for girls) or (2) a score equal to or above the cut-off (8) on one of the subscales.⁶⁹

Next, in patients with these subclinical symptoms, the Anxiety Disorders Interview Schedule—Child and Parent Version (ADIS-C/P)^{70 71} is administered by a research psychologist by telephone. Thereafter, the severity of depressive and/or anxiety symptoms is rated by the research psychologist using the Child Depression Rating Scale—Revised (CDRS-R; ages 10–12 years),⁷² the Adolescent Depression Rating Scale (ADRS; ages 13–20 years)⁷³ and the Pediatric Anxiety Rating Scale (PARS; ages 10–20 years).⁷⁴ Patients are excluded for randomisation if they meet criteria for a clinical depressive or anxiety disorder on the ADIS-C/P and score equal to or above the clinical cut-off on the CDRS (40),⁷⁵ ADRS (20)⁷³ or PARS (18).⁷⁴ Instead, these patients are referred for attuned psychological treatment, since it would be unethical to randomise them. For patients with subclinical depression and/or anxiety, the medical researcher performs the randomisation and arranges the medical baseline assessment.

All patients included in our study are well phenotyped with regard to duration and severity of disease, age at diagnosis, growth and pubertal development, clinical course of disease, number and type of surgical interventions and hospitalisations. The Paris classification is collected at diagnosis and from the most recent endoscopy, to see if extension of disease has occurred.

Randomisation and blinding

Patients are allocated to PASCET-PI or CAU group by means of computer-based, block randomisation, stratified per centre. Sealed envelopes sequentially numbered

are provided by the Department of Biostatistics of the Erasmus Medical Center. Participants assigned to the treatment group start treatment within a maximum of 4 weeks.

To prevent bias in the assessment, the research psychologist completing the diagnostic interviews at T0–T3 is blinded for the outcome of randomisation. In addition, physicians assessing the patient's disease activity are blinded. The patients and therapists are asked not to discuss the psychotherapy with the treating physician. Unblinding takes place if patients are excluded from the study (either by withdrawal or an acute need for care).

Intervention

The PASCET-PI focuses on behavioural activation, cognitive restructuring and problem-solving skills to change maladaptive behaviours, cognitions and coping strategies.⁶¹ Although originally designed to treat depression, most of the components of PASCET-PI are common for all CBT protocols, and have much overlap with components of CBT protocols specifically designed for anxiety (except for a fear hierarchy). Therefore, PASCET-PI can also be properly used for anxiety. Disease-specific components encompass the illness narrative (ie, perceptions and experience of having IBD), therapy for pain and immune functioning, disease-specific psychoeducation, social skills training and emphasis on IBD-related cognitions and behaviours. Parents are provided with psychoeducation about being a CBT-coach helping their child coping with IBD.^{17 89}

The PASCET-PI consists of 10 weekly sessions, delivered in 3 months (table 2). Six sessions are face to face (1 h), and four sessions are telephone sessions (30 min). Three parental sessions are held at the beginning, middle and end of treatment. For adult patients (≥18 years) who still live with their parents, this is recommended but voluntarily. Adult patients who do not live with their parents, participate without their parents. Thereafter, three 30 min booster sessions (one

**Table 2** Outline of the PASCET-PI⁶¹

Session number	Content of session
Session 1 <i>Live</i>	Introduction of ACT and THINK model and PASCET-PI, build alliance, psychoeducation about IBD and depression or anxiety, illness narrative
Session 2 <i>Live</i>	Mood monitoring, explaining link between feelings, thoughts and behaviours, discussing feeling good and feeling bad, problem-solving
Session 3 <i>By telephone</i>	Link between behaviour and feelings: Activities to feel better
Session 4 <i>Live</i>	Be Calm and confident: relaxation exercises
Session 5 <i>Live</i>	Be calm and Confident : positive self vs negative self, training social skills
Session 6 <i>By telephone</i>	Talents: developing talents and skills makes you feel better
Session 7 <i>Live</i>	Social problem solving, discussing the ACT skills and introduction of the THINK skills with discussing negative thoughts (Think positive)
Session 8 <i>By telephone</i>	Help from a friend, Identify the 'Silver Lining' and No replaying bad thoughts
Session 9 <i>By telephone</i>	Keep trying —don't give up, making several plans to use the ACT and THINK skills
Session 10 <i>Live</i>	Quiz on ACT and THINK model, discussing use of ACT and THINK skills in the future, updating illness narrative
Booster 1 <i>By telephone</i>	Several plans to use the ACT and THINK skills, updating illness narrative, personalising ACT and THINK skills
Booster 2 <i>By telephone</i>	Several plans to use the ACT and THINK skills, updating illness narrative, personalising ACT and THINK skills
Booster 3 <i>By telephone</i>	Several plans to use the ACT and THINK skills, updating illness narrative, personalising ACT and THINK skills
Family 1 <i>Live</i>	Parental view on IBD, family situation, psychoeducation about IBD and depression or anxiety, introduction of ACT and THINK model and PASCET-PI
Family 2 <i>Live</i>	Parental view on progress, the ACT and THINK skills that are most effective for patient, expressing emotions within family, family communication, family stress game
Family 3 <i>Live</i>	Parental view on progress, family communication, parental depression or anxiety

IBD, inflammatory bowel disease; PASCET-PI, Primary and Secondary Control Enhancement Training—Physical Illness.

per month) are provided by telephone. For the current study, the original PASCET-PI was translated into the Dutch language. During this study, patients will receive medical care according to the current guidelines. Psychological interventions, other than the PASCET-PI for the intervention group, are not allowed.

Training and protocol adherence

Before providing the PASCET-PI, all licensed (health-care) psychologists had followed a PASCET-PI training (developed and given by EMS). To prevent protocol drifting they receive monthly PASCET-PI supervision by a senior clinical psychologist. All treatment sessions are audiotaped, and a random 20% is rated by independent raters (senior clinical psychologist and master's Psychology students) using the PASCET-PI Protocol Adherence Checklist (PPAC).⁶³

Outcome measures

In table 1, an overview of all variables and instruments at each time point is provided, with informants specified. All the psychological questionnaires used are (inter) nationally validated instruments, for which psychometric properties have been established in the Netherlands. Owing to the lack of space, instruments for the main psychological and medical outcomes are described in detail below. Instruments for secondary outcomes and covariates are mentioned only. Covariates will be analysed as either confounder, mediator or moderator.

Main psychological outcome measures: changes in symptoms of depression and anxiety

Changes in symptoms of depression are assessed by the CDI and the BDI-II (to cover the complete age range). The CDI (used for ages 10–17 years) is a 27-item self-report scale (response categories 0–2: total score 0–54). It has excellent reliability (Cronbach's $\alpha > 0.85$), and moderate to good validity.⁶⁶ The BDI-II (used for ages 18–20 years) is a 21-item self-report scale (response categories 0–3: total score 0–63). The BDI-II has excellent reliability (Cronbach's $\alpha > 0.85$) and good to excellent validity.⁶⁷ In addition (changes in) the severity of the depressive symptoms will be rated with the CDRS-R or the ADRS. The CDRS-R (used for ages 10–12 years) is one of the most used rating scales for depression in children.⁷² The ADRS (used for ages 13–20 years) is developed specifically for adolescent depression.⁷³ Changes in symptoms of depression are analysed using Z-scores of CDI and BDI-II, and CDRS-R and ADRS.

Changes in symptoms of anxiety are assessed by the SCARED (used for ages 10–20 years), a 69-item screening instrument (response categories 0–2: total score 0–138) containing five subscales: general anxiety disorder, separation anxiety disorder, specific phobia, panic disorder and social phobia. Cronbach's α in the normative sample is 0.92 for the total score and between 0.66 and 0.87 for the subscales. Satisfactory concurrent validity has been shown.⁶⁸ In addition, changes in the severity of anxiety symptoms will be rated with the PARS,⁷⁴ for which a high internal consistency has been reported.⁷⁵

For both depression and anxiety, the semistructured interview ADIS-C/P (child and parent version) is administered. This diagnostic interview assesses diagnoses of depressive or anxiety disorders. Diagnostic and Statistical

Manual of Mental Disorders (DSM) IV symptoms are reviewed as either present ('Yes') or absent ('No').^{70 71}

Main medical outcome measure: sustained remission at 12 months

Sustained remission of IBD (absence of clinical relapse) is continued clinical remission with no relapses, without the need to escalate treatment, use of new induction treatment (except for the first 8 weeks after baseline), hospitalise or perform bowel surgery during the first 12 months. In case of active disease at the time of enrolment, sustained remission at 12 months means continued remission after 8 weeks of induction treatment starting at baseline. The PCDAI and the PUCAI are used to score disease activity, and to score remission or relapse. The PCDAI (for CD) is a validated, multi-item, physician-reported measure that comprises items on history (abdominal pain, stools, activity level), physical examination, height and weight, as well as laboratory parameters. Scores range from 0 to 100, with higher scores representing more active disease.^{90 91} The PUCAI is a clinical index on disease activity for UC, scored by the physician, which has been validated in multiple international drug studies and comprises items on abdominal pain, rectal bleeding, stool frequency and consistency and activity level. Scores range from 0 to 85, with higher scores representing more active disease.⁹² For patients with CD and UC, remission is defined as PCDAI <10 and PUCAI <10, respectively. For CD, relapse is defined as PCDAI >30 or an increase of >15 points and intensification of medical treatment. For UC, relapse is defined as PUCAI >34 or an increase of ≥ 20 points for UC and intensification of medical treatment.^{90 92 93}

Secondary outcomes

Secondary psychological outcomes are IBD-related quality of life and social functioning.

Secondary medical outcomes are disease activity, inflammatory markers in blood (C reactive protein) and stool (calprotectin), use of IBD medication and necessity of surgery (see [table 1](#)).

Psychological and medical covariates

Several factors associated with depression and anxiety in IBD (eg, IBS-like symptoms, cognitive coping, parental stress) will be assessed because they can confound, mediate or moderate the effect of CBT on medical and psychological outcomes. Psychological covariates assessed are: illness perception, cognitive coping, quality of sleep, parental anxiety and/or depression, stressful life events, family functioning, and demographic factors.

Medical covariates encompass: disease phenotype, treatment strategy, disease activity, and IBS-like symptoms. Blood samples for immunological analysis will be drawn at baseline and after 3 months. For cytokine analysis, one EDTA tube (10 mL) will be drawn. PBMCs will be isolated and the plasma stored at -80°C . Serum

levels of proinflammatory cytokines (TNF- α , IL-1, IL-1 β , IL-6, IL-8) will be assessed in plasma and supernatant of PBMCs in culture using, respectively, Cytokine Bead Analysis or ELISA. Furthermore, intracellular flow cytometry will be performed on in vitro-stimulated PBMCs. For the RNA expression analysis, 2.5 mL venous blood will be collected in PAXgene tubes (PreAnalytiX) and stored at -20°C until RNA extraction. Total cellular RNA will be extracted using the PAXgeneTM blood RNA kit (Qiagen) according to the manufacturer's protocol. Gene expression profiles of proinflammatory and anti-inflammatory genes in peripheral blood leucocytes will be assessed by Affymetrix U133 2.0 plus GeneChips.

Data collection: follow-up assessments

Follow-up assessments take place at similar moments in the CBT and CAU group: 3 (T1), 6 (T2) and 12 (T3) months after randomisation. Each follow-up assessment consists of a regular medical visit and a psychological assessment (online questionnaires and diagnostic psychiatric interview) for the patient and, if applicable, parents. Patients with a clinical depressive or anxiety disorder (according to the same criteria as at baseline), or with an urgent need of psychological help, are excluded. To ensure participation throughout the study, patients receive a small reward after completing the last follow-up assessment.

Withdrawal

Patients can withdraw from the study without any consequences at any time for any reason. Those who withdraw are asked to complete the follow-up assessments.

Sample size

The target population is a group of approximately 350 patients with IBD aged 10–20 years. Basing on our previous studies concerning psychological problems in physically ill adolescents, the expected response rate will be above 80%,⁹⁴ which corresponds with ± 280 patients. Basing on literature, around 40% of adolescents with IBD will suffer from increased symptoms of depression or anxiety. Of those patients 10% will experience clinical depression or anxiety. Of the remaining ± 100 patients, 50 patients will be randomised to the treatment condition (CBT and CAU) and 50 to CAU. Sample size is based on two-tailed tests with size of $\alpha=0.05$ using a repeated measures design with estimated correlation between time points of 0.6. For the effect of CBT on symptoms of depression, small-effect to medium-effect sizes are expected (Cohen's $d > 0.3$),^{95 96} for the effect on symptoms of anxiety medium-effect to large-effect sizes are expected (Cohen's $d > 0.6$).^{97 98} For the effect of CBT on sustainment of remission (no clinical relapse), a medium-effect size is expected ($\omega=0.3$). Basing on clinical experience in our hospital, in the CAU group, 40% of patients will have sustained remission during 12 months. We hypothesise that 70% of



patients will have sustained remission in the treatment group, reflecting a medium-effect size. Using the target population of N=100 and the estimated effects on depression, anxiety and sustainment of remission, we will have sufficient power (>0.85).

Statistical analyses

The main analyses will be conducted using an intention-to-treat approach. Where appropriate, secondary analysis will be conducted using a per-protocol basis. To test the effectiveness of the PASCET-PI, we will compare the CBT group with the CAU group on (1) change in symptoms of depression and anxiety and (2) sustained remission (absence of clinical relapse). For (1) multilevel linear models will be used, for (2) a generalised estimating equation (GEE) approach will be used. Covariates (eg, illness perception, cognitive coping, disease phenotypes, medical treatment strategy, inflammatory markers) will be included into the multilevel linear models and the GEE to identify which factors influence the effectiveness of the disease-specific CBT. Multiple imputation will be used to deal with missing values.

DISCUSSION

PASCET-PI has proven to be effective in reducing depression in adolescents with IBD. However, the effect on anxiety, quality of life and disease course has hardly been studied systematically. We will perform a prospective RCT to examine the effectiveness of the PASCET-PI on both symptoms of depression *and* anxiety, on quality of life, and on clinical course of the inflammatory disease.

This study has several strengths. First, as this study examines the effect of disease-specific CBT on both psychological problems *and* disease course, it will provide insight to the complex interplay between inflammation and depression or anxiety in paediatric patients. We will study possible effects of reduction in depression or anxiety on cytokine expression and RNA expression profiles before and after CBT for subclinical depression or anxiety. Second, the disease-specific CBT will target both depression and anxiety, which is important, as these problems have a negative impact on medication adherence and long-term medical and psychological outcomes.^{16 19 23 24 29 45–47} Third, this study will provide important information about the prevalence of depression and anxiety among adolescents with IBD in an European country, such as the Netherlands, as compared to other studies that were performed mainly in the USA. Cultural differences may play a role in coping with disease-related anxiety and depression. Fourth, the PASCET-PI encompasses IBD-specific components, which matches patients' IBD-related concerns and problems very well. If proven effective, the PASCET-PI can be very helpful for treatment of current and also for prevention of future psychological problems. A fifth strength of the study is the random and longitudinal

nature of the design. Patients will be randomly assigned to the experimental or control condition. It is known that academic hospitals treat more severe IBD cases than community hospitals. Therefore, the randomisation will be stratified for academic versus community hospitals. Randomised patients will complete several follow-up assessments, which allows us to evaluate long-term effects of the PASCET-PI.

In conclusion, there is a compelling need to improve the emotional well-being of the adolescents with IBD who suffer from (subclinical) depression or anxiety symptoms. If the PASCET-PI proves to be effective in treating both subclinical depression and anxiety, in improving quality of life, and in preventing clinical relapse, screening for and treatment of psychological problems in adolescents with IBD should be incorporated in standard care.

Author affiliations

¹Department of Pediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

²Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

³Department of Midwifery Science, AVAG and the EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands

⁴Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Contributors JCE and EMWJU designed and supervised the trial. HEM and JH wrote the grant proposals and helped in designing the trial. GvdB and LS drafted this paper, which was edited and modified by JCE, EMWJU, EMS, HEM and JH. EMWJU translated the PASCET-PI treatment manual and is responsible for supervision of the psychologists. EMS also contributed to the design of the trial and trained the psychologists on-site. All authors read and approved the final manuscript.

Funding This research is externally funded by grant applications of the following non-commercial Dutch foundations: Stichting Theia (grant number 2013201), Fonds NutsOhra (grant number 1303-012), Stichting Crohn en Colitis Ulcerosa Fonds Nederland (grant number 14.307.04), Stichting Vrienden van het Sophia. The funders did not have any influence in the design and execution of the trial.

Competing interests None declared.

Ethics approval The study is approved by the Medical Ethics Committee of the Erasmus MC and confirmed by the institutional ethics review committees of the participating hospitals. All study data and human material will be handled confidentially and coded with a unique study number. Only the research team will have access to the data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

1. Baumgart DC, Bernstein CN, Abbas Z, *et al*. IBD around the world: comparing the epidemiology, diagnosis, and treatment: proceedings of the World Digestive Health Day 2010—Inflammatory Bowel Disease Task Force meeting. *Inflamm Bowel Dis* 2011;17:639–44.

2. Greenley RN, Hommel KA, Nebel J, *et al.* A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. *J Pediatr Psychol* 2010;35:857–69.
3. Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol* 2004;18:509–23.
4. Rabizadeh S, Dubinsky M. Update in pediatric inflammatory bowel disease. *Rheum Dis Clin North Am* 2013;39:789–99.
5. Engelman G, Erhard D, Petersen M, *et al.* Health-related quality of life in adolescents with inflammatory bowel disease depends on disease activity and psychiatric comorbidity. *Child Psychiatry Hum Dev* 2015;46:300–7.
6. Lynch T, Spence D. A qualitative study of youth living with Crohn disease. *Gastroenterol Nurs* 2008;31:224–30; quiz 31–2.
7. Kilroy S, Nolan E, Sarma KM. Quality of life and level of anxiety in youths with inflammatory bowel disease in Ireland. *J Pediatr Gastroenterol Nutr* 2011;53:275–9.
8. Ross SC, Strachan J, Russell RK, *et al.* Psychosocial functioning and health-related quality of life in paediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2011;53:480–8.
9. Karwowski CA, Keljo D, Szigethy E. Strategies to improve quality of life in adolescents with inflammatory bowel disease. *Inflamm Bowel Dis* 2009;15:1755–64.
10. Mackner LM, Greenley RN, Szigethy E, *et al.* Psychosocial issues in pediatric inflammatory bowel disease: report of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2013;56:449–58.
11. Szigethy E, Craig AE, Iobst EA, *et al.* Profile of depression in adolescents with inflammatory bowel disease: implications for treatment. *Inflamm Bowel Dis* 2009;15:69–74.
12. Szigethy E, McLafferty L, Goyal A. Inflammatory bowel disease. *Pediatr Clin North Am* 2011;58:903–20, x–xi.
13. Burke P, Meyer V, Kocoshis S, *et al.* Depression and anxiety in pediatric inflammatory bowel disease and cystic fibrosis. *J Am Acad Child Adolesc Psychiatry* 1989;28:948–51.
14. Burke PM, Neigut D, Kocoshis S, *et al.* Correlates of depression in new onset pediatric inflammatory bowel disease. *Child Psychiatry Hum Dev* 1994;24:275–83.
15. Clark JG, Srinath AI, Youk AO, *et al.* Predictors of depression in youth with Crohn disease. *J Pediatr Gastroenterol Nutr* 2014;58:569–73.
16. Reigada LC, Bruzzese JM, Benkov KJ, *et al.* Illness-specific anxiety: implications for functioning and utilization of medical services in adolescents with inflammatory bowel disease. *J Spec Pediatr Nurs* 2011;16:207–15.
17. Szigethy E, Kenney E, Carpenter J, *et al.* Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. *J Am Acad Child Adolesc Psychiatry* 2007;46:1290–8.
18. Szigethy E, Levy-Warren A, Whitton S, *et al.* Depressive symptoms and inflammatory bowel disease in children and adolescents: a cross-sectional study. *J Pediatr Gastroenterol Nutr* 2004;39:395–403.
19. Reigada LC, Hoogendoorn CJ, Walsh LC, *et al.* Anxiety symptoms and disease severity in children and adolescents with Crohn disease. *J Pediatr Gastroenterol Nutr* 2015;60:30–5.
20. Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. *Depress Anxiety* 2001;14:67–78.
21. Mikocka-Walus AA, Turnbull DA, Moulding NT, *et al.* Controversies surrounding the comorbidity of depression and anxiety in inflammatory bowel disease patients: a literature review. *Inflamm Bowel Dis* 2007;13:225–34.
22. Copeland WE, Shanahan L, Costello EJ, *et al.* Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry* 2009;66:764–72.
23. Thompson RD, Craig A, Crawford EA, *et al.* Longitudinal results of cognitive behavioral treatment for youths with inflammatory bowel disease and depressive symptoms. *J Clin Psychol Med Settings* 2012;19:329–37.
24. Loftus EV Jr, Guerin A, Yu AP, *et al.* Increased risks of developing anxiety and depression in young patients with Crohn's disease. *Am J Gastroenterol* 2011;106:1670–7.
25. Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology* 2013;144:36–49.
26. Goodhand JR, Wahed M, Mawdsley JE, *et al.* Mood disorders in inflammatory bowel disease: relation to diagnosis, disease activity, perceived stress, and other factors. *Inflamm Bowel Dis* 2012;18:2301–9.
27. Bennebroek Evertsz F, Thijssens NA, Stokkers PC, *et al.* Do inflammatory bowel disease patients with anxiety and depressive symptoms receive the care they need? *J Crohns Colitis* 2012;6:68–76.
28. Panara AJ, Yarur AJ, Rieders B, *et al.* The incidence and risk factors for developing depression after being diagnosed with inflammatory bowel disease: a cohort study. *Aliment Pharm Ther* 2014;39:802–10.
29. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflamm Bowel Dis* 2009;15:1105–18.
30. Mittermaier C, Dejaco C, Waldhoer T, *et al.* Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. *Psychosom Med* 2004;66:79–84.
31. Nahon S, Lahmek P, Durance C, *et al.* Risk factors of anxiety and depression in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;18:2086–91.
32. Keethy D, Mrakotsky C, Szigethy E. Pediatric inflammatory bowel disease and depression: treatment implications. *Curr Opin Pediatr* 2014;26:561–7.
33. Simren M, Axelsson J, Gillberg R, *et al.* Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* 2002;97:389–96.
34. Engstrom I. Inflammatory bowel disease in children and adolescents: mental health and family functioning. *J Pediatr Gastroenterol Nutr* 1999;28:S28–33.
35. Gray WN, Graef DM, Schuman SS, *et al.* Parenting stress in pediatric IBD: relations with child psychopathology, family functioning, and disease severity. *J Dev Behav Pediatr* 2013;34:237–44.
36. Fuller-Thomson E, Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. *Inflamm Bowel Dis* 2006;12:697–707.
37. Mackner LM, Crandall WV. Psychological factors affecting pediatric inflammatory bowel disease. *Curr Opin Pediatr* 2007;19:548–52.
38. Szigethy EM, Youk AO, Benhayon D, *et al.* Depression subtypes in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2014;58:574–81.
39. Reed-Knight B, Lobato D, Hagin S, *et al.* Depressive symptoms in youth with inflammatory bowel disease compared with a community sample. *Inflamm Bowel Dis* 2014;20:614–21.
40. Bernstein CN, Singh S, Graff LA, *et al.* A prospective population-based study of triggers of symptomatic flares in IBD. *Am J Gastroenterol* 2010;105:1994–2002.
41. Bitton A, Dobkin PL, Edwardes MD, *et al.* Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut* 2008;57:1386–92.
42. Bitton A, Sewitch MJ, Peppercorn MA, *et al.* Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. *Am J Gastroenterol* 2003;98:2203–8.
43. Levenstein S, Prantera C, Varvo V, *et al.* Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. *Am J Gastroenterol* 2000;95:1213–20.
44. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut* 2005;54:1481–91.
45. Srinath AI, Goyal A, Zimmerman LA, *et al.* Predictors of abdominal pain in depressed pediatric inflammatory bowel disease patients. *Inflamm Bowel Dis* 2014;20:1329–40.
46. Ryan JL, Mellon MW, Junger KW, *et al.* The clinical utility of health-related quality of life screening in a pediatric inflammatory bowel disease clinic. *Inflamm Bowel Dis* 2013;19:2666–72.
47. Gray WN, Denson LA, Baldassano RN, *et al.* Treatment adherence in adolescents with inflammatory bowel disease: the collective impact of barriers to adherence and anxiety/depressive symptoms. *J Pediatr Psychol* 2012;37:282–91.
48. O'Donovan A. Inflammation and depression: unraveling the complex interplay in inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2014;58:541–2.
49. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* 2006;27:24–31.
50. Mawdsley JE, Rampton DS. The role of psychological stress in inflammatory bowel disease. *Neuroimmunomodulation* 2006;13:327–36.
51. Reber SO. Stress and animal models of inflammatory bowel disease—an update on the role of the hypothalamo-pituitary-adrenal axis. *Psychoneuroendocrinology* 2012;37:1–19.
52. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol Bull* 2014;140:774–815.

53. Penninx BW, Milaneschi Y, Lamers F, *et al.* Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Med* 2013;11:129.
54. Schmidt HD, Shelton RC, Duman RS. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. *Neuropsychopharmacology* 2011;36:2375–94.
55. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med* 2009;71:171–86.
56. Dowlati Y, Herrmann N, Swardfager W, *et al.* A meta-analysis of cytokines in major depression. *Biol Psychiatry* 2010;67:446–57.
57. Vogelzangs N, Beekman AT, de Jonge P, *et al.* Anxiety disorders and inflammation in a large adult cohort. *Transl Psychiatry* 2013;3:e249.
58. Hou R, Baldwin DS. A neuroimmunological perspective on anxiety disorders. *Hum Psychopharmacol* 2012;27:6–14.
59. Salim S, Chugh G, Asghar M. Inflammation in anxiety. *Adv Protein Chem Struct Biol* 2012;88:1–25.
60. Hoge EA, Brandstetter K, Moshier S, *et al.* Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depress Anxiety* 2009;26:447–55.
61. Szigethy E, Weisz JR, Findling RL. *Cognitive-behavior therapy for children and adolescents*. Arlington: American Psychiatric Publishing, 2012:331–78.
62. Thompson RD, Delaney P, Flores I, *et al.* Cognitive-behavioral therapy for children with comorbid physical illness. *Child Adolesc Psychiatr Clin N Am* 2011;20:329–48.
63. Szigethy E, Whitton SW, Levy-Warren A, *et al.* Cognitive-behavioral therapy for depression in adolescents with inflammatory bowel disease: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2004;43:1469–77.
64. Szigethy E, Bujoreanu SI, Youk AO, *et al.* Randomized efficacy trial of two psychotherapies for depression in youth with inflammatory bowel disease. *J Am Acad Child Adolesc Psychiatry* 2014;53:726–35.
65. Reigada LC, Benkov KJ, Bruzzese JM, *et al.* Integrating illness concerns into cognitive behavioral therapy for children and adolescents with inflammatory bowel disease and co-occurring anxiety. *J Spec Pediatr Nurs* 2013;18:133–43.
66. Timbremont B, Brat C, Roelofs J. *Handleiding children's depression inventory (herziene versie)*. Amsterdam, NL: Pearson, 2008.
67. van der Does AJW. *BDI-II-NL. Handleiding. De Nederlandse versie van de Beck Depression Inventory*. Lisse, NL: Harcourt Test Publishers, 2002.
68. Muris P, Bodden D, Hale W, *et al.* *Vragenlijst over angst en bang zijn bij kinderen en adolescenten. Handleiding bij gereviseerde Nederlandse versie van de Screen for Child Anxiety Related Disorders*. Amsterdam, NL: Boom, 2007.
69. Bodden DH, Bogels SM, Muris P. The diagnostic utility of the Screen for Child Anxiety Related Emotional Disorders-71 (SCARED-71). *Behav Res Ther* 2009;47:418–25.
70. Siebelink BM, Treffers PDA. *Anxiety disorders interview schedule for DSM-IV-child version, ADIS-C Handleiding*. Amsterdam: Harcourt Test Publishers, 2001.
71. Silverman WK, Albano AM. *Anxiety disorders interview schedule for DSM-IV child version, child interview schedule*. San Antonio: The Psychological Corporation, 1996.
72. Poznanski EO, Mokros H. *Children's depression rating scale revised (CDRS-R)*. Los Angeles: Western Psychological Services, 1996.
73. Revah-Levy A, Birmaher B, Gasquet I, *et al.* The Adolescent Depression Rating Scale (ADRS): a validation study. *BMC Psychiatry* 2007;7:2.
74. No authors listed. The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties. *J Am Acad Child Adolesc Psychiatry* 2002;41:1061–9.
75. Ginsburg GS, Keeton CP, Drazdowski TK, *et al.* The utility of clinicians ratings of anxiety using the Pediatric Anxiety Rating Scale (PARS). *Child Youth Care For* 2011;40:93–105.
76. Vogels T, Verrips GHW, Koopman HM, *et al.* *Child Quality of Life Questionnaire (TACQOL). Manual parent and child form*. Leiden, NL: LUMC-TNO, 1999.
77. Bruil J, Fekkes M, Vogels T, *et al.* *TAAQOL Manual*. Leiden, NL: Leiden Center for Child Health and Pediatrics LUMC-TNO, 2004.
78. Loonen HJ, Grootenhuys MA, Last BF, *et al.* Measuring quality of life in children with inflammatory bowel disease: the impact-II (NL). *Qual Life Res* 2002;11:47–56.
79. Liber JM, Van Lang NDJ, Treffers PDA. *Confirmatory factor analysis of the Dutch version of the Social Skills Rating System: Curium, Academic Center for Child and Adolescent Psychiatry*. LUMC, 2006.
80. Achenbach TM, Rescorla LA. *Manual for the ASEBA school-age forms & profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families, 2001.
81. Achenbach TM, Rescorla LA. *Manual for the ASEBA Adult Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families, 2003.
82. Utens EMWJ, van Rijen EHM, Erdman RAM, *et al.* *Rotterdam's Kwaliteit van Leven Interview: Erasmus MC Rotterdam, Netherlands*. Department of Child and Adolescent Psychiatry and Psychology, 2000.
83. Broadbent E, Petrie KJ, Main J, *et al.* The brief illness perception questionnaire. *J Psychosom Res* 2006;60:631–7.
84. Garnefski N, Kraaij V, Spinhoven P. *CERQ: Manual for the use of the cognitive emotion regulation questionnaire. A questionnaire for measuring cognitive coping strategies*. Leiderdorp, NL: Datec V.O.F., 2007.
85. Owens JA, Spirito A, McGuinn M, *et al.* Sleep habits and sleep disturbance in elementary school-aged children. *J Dev Behav Pediatr* 2000;21:27–36.
86. Beurs E, Van Dyck R, Marquenie LA, *et al.* De DASS: een vragenlijst voor het meten van depressie, angst en stress. *Gedragstherapie* 2001;34:35–53.
87. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE. Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. *Cancer* 2008;113:870–8.
88. Epstein NB, Baldwin LM, Bishop DS. The McMaster family assessment device. *J Marital Fam Ther* 1983;9:171–80.
89. Weisz JR, Thurber CA, Sweeney L, *et al.* Brief treatment of mild-to-moderate child depression using primary and secondary control enhancement training. *J Consult Clin Psychol* 1997;65:703–7.
90. Hyams JS, Ferry GD, Mandel FS, *et al.* Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr* 1991;12:439–47.
91. Turner D, Griffiths AM, Walters TD, *et al.* Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. *Inflamm Bowel Dis* 2012;18:55–62.
92. Turner D, Otley AR, Mack D, *et al.* Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007;133:423–32.
93. Hyams J, Crandall W, Kugathasan S, *et al.* Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007;132:863–73; quiz 1165–6.
94. Utens EM, Verhulst FC, Duivenvoorden HJ, *et al.* Prediction of behavioural and emotional problems in children and adolescents with operated congenital heart disease. *Eur Heart J* 1998;19:801–7.
95. Klein JB, Jacobs RH, Reinecke MA. Cognitive-behavioral therapy for adolescent depression: a meta-analytic investigation of changes in effect-size estimates. *J Am Acad Child Adolesc Psychiatry* 2007;46:1403–13.
96. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull* 2006;132:132–49.
97. In-Albon T, Schneider S. Psychotherapy of childhood anxiety disorders: a meta-analysis. *Psychother Psychosom* 2007;76:15–24.
98. Reynolds S, Wilson C, Austin J, *et al.* Effects of psychotherapy for anxiety in children and adolescents: a meta-analytic review. *Clin Psychol Rev* 2012;32:251–62.